

FORMULARIO UNICO DE OPOSICION

①

OPOSICIÓN A:

- | | | | |
|-------------------------------------|---|--------------------------|-------------------------|
| ☒ | Patente de Invención. | ☐ | Marca Colectiva. |
| ☐ | Patente de Modelo de Utilidad. | ☐ | Marca de Certificación. |
| ☐ | Diseño Industrial. | ☐ | Lema Comercial. |
| ☐ | Esquema de Trazado para Circuitos Integrados. | | |
| ☐ | Marcas de Productos o Servicios. | | |

②

Número del expediente: 07 136836

Solicitante: BIOVAIL LABORATORIES INTERNATIONAL SRL

**SOLICITUD
PUBLICADA**

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: **FORMULACIONES DE UNA SAL DE BUPROPION DE LIBERACION MODIFICADA**

Gaceta: 612

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: **GYNOPHARM S.A.**

Dirección: Carrera 14 N° 94-44 Piso 7 Torre b

Nacionalidad o Domicilio: **COLOMBIA**
Lugar de Constitución: **BARRANQUILLA**

Telefono: **2 36 84 95** Fax:
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 802, 006,279-4

**REPRESENTANTE
O APODERADO**

Nombre: **CIELO ANGELA PEÑA
RODRIGUEZ**

Dirección: **CARRERA 13 No. 119-95**

Teléfono: (571) 213 12 13 Fax: (571) 612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 51.940.252 TP 82701

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo “Fundamento de Hechos”.

⑤ Comprobante de pago No. _____

Fecha _____

2
1209

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: _____

C.C. 51.940.252

TP. 82701

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07 136836 ✓
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIONES DE UNA SAL DE BUPROPION DE
LIBERACIÓN MODIFICADA."
Solicitante : BIOVAIL LABORATORIES INTERNATIONAL S.R.L.
Opositora : GYNOPHARM S.A.

Publicada en la ~~Gaceta~~ de la Propiedad Industrial
N° 612 del 29 de enero de 2010

Yo, **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **82701** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMULACIONES DE UNA SAL DE BUPROPION DE LIBERACIÓN MODIFICADA", cuyo titular es **BIOVAIL LABORATORIES INTERNATIONAL S.R.L.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular una sal de bupropion. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 27 de diciembre de 2007 reivindicando prioridad bajo la solicitud WO2006US24832 del 2006-06-27 ; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010, cuya publicación internacional corresponde a la WO 2007/002597 del 2007-01-04.

2.2. La solicitud colombiana 07 136836 objeto de la presente oposición, se refiere a una composición adecuada para la administración a un sujeto que necesita tratamiento para una afección, que comprende: una cantidad farmacéuticamente eficaz de sal bromhidrato de bupropion, donde dicha composición de bromhidrato de bupropion es más estable que una composición correspondiente que comprende clorhidrato de bupropion; donde dicha composición es adecuada para la

administración oral a un sujeto que necesita la administración de bupropion; donde dicha composición de bromhidrato de bupropion es más estable que una composición, por lo demás equivalente, de clorhidrato de bupropion cuando se la almacena durante al menos 3 meses a 40 grados C y 75% de humedad relativa; donde es más estable cuando se la almacena durante al menos 6 meses a 40 grados C y 75 % de humedad relativa; donde contiene menos de al menos un producto de degradación característico de la degradación de bupropion después de haber sido almacenada a 40 grados C a 75% de humedad relativa que una composición, por lo demás similar, de clorhidrato de bupropion almacenada en las mismas condiciones; y, donde presenta menos fluctuaciones en el perfil de la disolución in vitro en al menos un medio de disolución que otra composición, por lo demás equivalente, de clorhidrato de bupropion después de haber sido almacenadas durante al menos 3 meses a 40 grados C y 75 % de humedad relativa.

2.3. En primera instancia, se debe advertir que algunas reivindicaciones también se refieren a un uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel*

inventivo y sean susceptibles de aplicación industrial". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO9938502 publicada el 5 de agosto de 1999.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela métodos y composiciones que utilizan un (+)-isómero de bupropión ópticamente puro, como medicamento para el tratamiento de la depresión, la enfermedad de Parkinson, obesidad, aumento de peso, bipolaridad, para déficit de atención o trastornos de la conducta, la disfunción físico-sexual, bulimia, trastornos de la alimentación o ansia por la comida, donde según este documento D1, la composición se puede administrar por vía intravenosa, transdérmica (parches) o por vía oral, posiblemente en una forma de liberación sostenida. A partir de este documento anterior, cualquier persona versada en la materia podría de manera evidente llegar por deducción a formulaciones con una cantidad farmacéuticamente eficaz de sal bromhidrato de bupropion, donde dicha composición de bromhidrato de bupropion es más estable que una composición correspondiente que comprende clorhidrato de bupropion, pues esta anterioridad también se refiere a una composición que comprende cantidad farmacéuticamente eficaz de una sal de hidrobromuro de bupropion en diversas formas, incluido como enantiómeros y polimorfos y en combinación con otras drogas. Igualmente este documento D1, enseña composiciones que comprenden cantidades efectiva farmacéuticamente de una sal de hidrocloreto de bupropion en una forma enantiomérica y en formas cristalinas, según se indica en el documento, en especial las páginas 7 y 9. Particularmente, esta anterioridad D1 también enseña que las distintas vías de

administración son conocidas en el arte y enseñanza expresamente que la sal de hidrobromuro se puede obtener con base en lo que define en la página 14, línea 11. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no comprende altura o nivel inventivo pues lo revelado ya se deriva evidentemente del estado de la técnica

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 136836 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 27 de junio de 2006, a partir del documento D1, puede llegar de manera evidente a una cantidad farmacéuticamente eficaz de sal bromhidrato de bupropion, donde dicha composición de bromhidrato de bupropion es más estable que una composición correspondiente que comprende clorhidrato de bupropion, sobre el cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de*

aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."* La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **"FORMULACIONES DE UNA SAL DE BUPROPION DE LIBERACIÓN MODIFICADA"**, cuyo titular es **BIOVAIL LABORATORIES INTERNATIONAL S.R.L**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO9938502 publicada el 5 de agosto de 1999.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

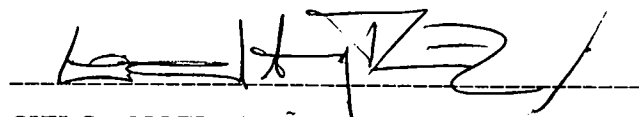
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: WO9938502 publicada el 5 de agosto de 1999.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

1018

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-136836-00005-0000

Fecha: 2010-04-27 11:13:41 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 44

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 32,638
FECHA : ABRIL 27 DE 2010

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	173531245	12/04/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	173531256	12/04/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	173531260	12/04/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	175496020	12/04/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	175496926	12/04/2010	295,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	295,000.00
	TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para presentar ante ese Despacho una remisión de información a la solicitud de patente No. 07 136836, titulada "FORMULACIONES DE UNA SAL DE BUPROPION DE LIBERACIÓN MODIFICADA", cuyo titular es **BIOVAIL LABORATORIES INTERNATIONAL S.R.L.**, publicada en la gaceta No. 612 del 29 de enero de 2010.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de dicha remisión, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en _____ (Colombia) a los **09 ABR 2010** días del mes de ____ de 2010.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.2194

Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.





DILIGENCIA DE RECONOCIMIENTO

Comparación ante el Notario 13 del Circuito de Bogotá.

quien exhibió la C.E. 319788.

Expedida en y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

BOGOTÁ, D.C.

09 ABR 2010



EL NOTARIO



HUELLA DEL INDICE DERECHO

NOTARIA DIECIOCHO DEL CÍRCULO DE BOGOTÁ D.C.
LA HUELLA SE AUTENTICA POR SOLICITUD DEL INTERESADO





01



* 9 0 7 3 5 0 2 0 *

1020

13

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/04/08

HORA: 15:57:11

OPERACION: 01JES0408254

PAGINA: 1

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303718-3303716.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada CYNOPHARM S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

CYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 902.006.272-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

Correo

electrónico:

mvenegas@gynopharm.com.co

Pagina Web:

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijó hasta el

*** CONTINUA ***

CERTIFICADO

CAMARA DE COMERCIO DE BUENOS AIRES

FECHA: 2010-04-08

HORA: 11:11:11

OPERACION: 0 480410134

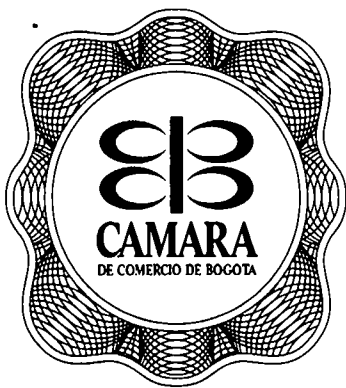
ACTIVA: 0

16 de Dic/bre de 2047.

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de pastillas y otros productos similares a partir de materiales tales como gelatinas y otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, así como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de instrumentos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica, en especial con cualquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoría y consultoria en las areas administrativa, de mercadeo, marketing, finanzas, la tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de SYNOQUARY S.A., así como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Comprar, vender, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion y comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad para tomar interes social como accionista, por lo tanto, para que tengan igual o similar objeto; comprar, vender, importar, exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar los

*** CORTEZA ***



01



* 9 0 7 3 5 0 2 1 *

1021

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/04/08

HORA: 15:57:11

OPERACION: 01UES0408254

PAGINA: 3

operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de títulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el país y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor protección de sus intereses corporativos o lo de sus socios.-----

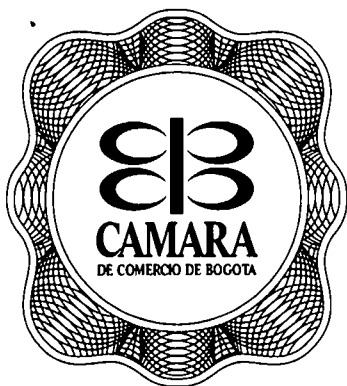
C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****4,000,000,000	*****4,000,000	*****1,000
Suscrito		
\$*****2,672,646,000	*****2,672,646	*****1,000
Pagado		
\$*****2,672,646,000	*****2,672,646	*****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Uni-

*** CONTINUA ***



01



90735022

1022

70

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/04/08

HORA: 15:57:11

OPERACION: 01JES0408254

PAGINA: 5

Fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Palacios Aragon Luis Alberto	CE.*****319,788

C E R T I F I C A

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*****351,283

C E R T I F I C A

Que según Acta No. 49 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal.	
PENALOSA AUDITORES & ASOCIADOS S.A.	Ni.*****830,095,635

C E R T I F I C A

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogota por Penalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Designado: Revisor Fiscal Ppal	
Padilla Borrero Ivan Dario	CC.*****80,025,798
Designado: Revisor Fiscal Suplente	
Comex Preciado Clara Judith	CC.*****52,544,226

C E R T I F I C A

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Cámara de Comercio el 23 de Noviembre del 2.000 bajo

*** CONTINUA ***

IMPRESO POR: [illegible]

CONTINUA DEL ANTERIOR

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/04/08

HORA: 15:57:11

OPERACION: O. ESCRITURA

PAGINA: 6

el No. 1.872 del libro respectivo, consta que el señor SUBER HILARI GONTOVNIK C.C. No. 19.463.982, actuando como Representante y Representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32-732.070, para que en nombre y representación de la sociedad suscriba todas las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones ordinarias.

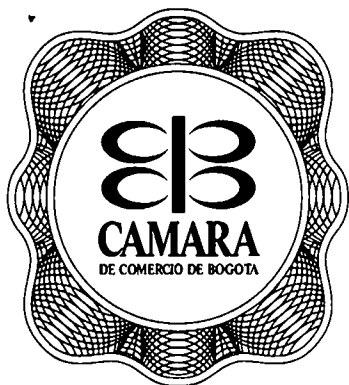
C E R T I F I C A

Que según Documento Privado de fecha 10 de octubre de 2000, inscrito en esta Cámara de Comercio, bajo el No. 1.872 del libro respectivo, consta que el señor SUBER HILARI GONTOVNIK, identificado con C.C. No. 19.463.982, actuando como Representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con cedula de ciudadanía No. 32.732.070 de Barranquilla, para que en representación de GYNOPHARM S.A., suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones ordinarias.

C E R T I F I C A

Que por Escritura Pública No. 2, de fecha 15 de Mayo de 2000, otorgada en la Notaria 1a. de Bogotá cuya parte pertinente se inscribió en esta Cámara de Comercio, el 32 de Julio de 2000 bajo el No. 3,948 del libro respectivo, consta que el señor LUIS ALBERTO ROMERO CERON C.C. No. 19.463.982, en su calidad de Representante legal de GYNOPHARM S.A., manifiesta que confiere poder general, amplio y suficiente a la señora CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadanía numero 52.352.190, para que en nombre de la sociedad GYNOPHARM S.A., promueva y defienda los intereses de esta sociedad, judicial y extrajudicialmente, en toda especie de gestiones y asuntos ante las autoridades administrativas o judiciales, para: a) Recibir notificaciones de cualquiera tipo de actos emanados de las autoridades administrativas o judiciales. b) Promover

*** CONTINUA ***



01



* 9 0 7 3 5 0 2 3 *

1023

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/04/08

HORA: 15:57:11

OPERACION: 01JES0408254

PAGINA: 7

Presentar recursos por la vía administrativa o judicial, renunciar a términos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar información a las autoridades administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.*****

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

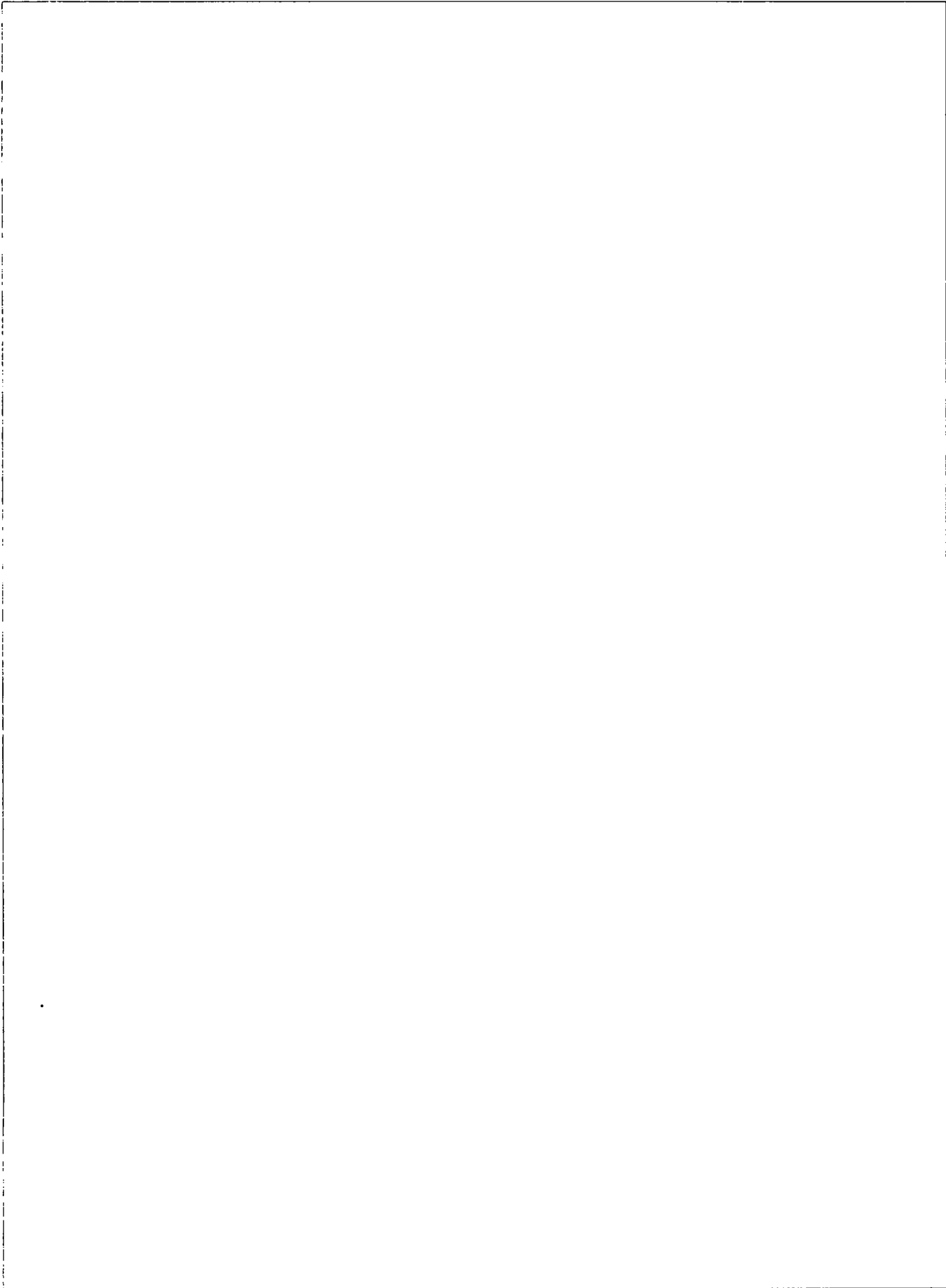
Que su última Renovación fue el: 31 de Marzo de 2010.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. rayar



17
1074



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/135		A1	(11) International Publication Number: WO 99/38502
			(43) International Publication Date: 5 August 1999 (05.08.99)
(21) International Application Number: PCT/US99/01952 (22) International Filing Date: 28 January 1999 (28.01.99) (30) Priority Data: 60/072,955 29 January 1998 (29.01.98) US (71) Applicant: SEPRACOR INC. [US/US]; 111 Locke Drive, Marlborough, MA 01752 (US). (72) Inventor: YOUNG, James, W.; 765 Talisman Court, Palo Alto, CA 94303 (US). (74) Agents: LAWRENCE, Stanton, T., III. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>	
(54) Title: PHARMACEUTICAL USES OF OPTICALLY PURE (+)-BUPROPION			
(57) Abstract			
Methods and compositions are disclosed utilizing the optically pure (+)-isomer of bupropion, which is a potent drug for treating depression, Parkinson's disease, obesity, weight gain, bipolar, attention-deficit or conduct disorders, phychosexual dysfunction, bulima, eating disorders or specific food craving. The composition can be administered intravenously, transdermally (patch) or orally, possibly in a sustained release form.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PHARMACEUTICAL USES OF OPTICALLY PURE (+) -BUPROPION

1. FIELD OF THE INVENTION

5 This invention relates to methods of treatment and pharmaceutical compositions employing the compound (+) - bupropion.

2. BACKGROUND OF THE INVENTION10 2.1. STERIC RELATIONSHIPS AND DRUG ACTION

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote
15 the absolute configuration of the molecule about its chiral center(s). The prefixes (+) and (-) or d and l are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is
20 dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric or
25 racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals, where 16 of the 20 most prescribed drugs exhibit chirality. A case in point is provided by the L-form of the β -adrenergic blocking agent, propranolol, which is
30 known to be 100 times more potent than the D-enantiomer.

Furthermore, optical purity is important since certain isomers may actually be deleterious rather than simply inert. For example, it has been suggested that the D-enantiomer of thalidomide was a safe and effective sedative
35 when prescribed for the control of morning sickness during pregnancy, while the corresponding L-enantiomer was a potent teratogen.

20
10-7

Bupropion is available only as a racemic mixture called Wellbutrin® and Wellbutrin SR® (for depression), and Zyban® (to achieve smoking cessation). That is, bupropion is available as a mixture of optical isomers, called
5 enantiomers. The racemic mixture of bupropion which is commercially available is administered as a hydrochloride salt. In addition, European Patent Application No. 84101070.5 published September 12, 1984 discloses the benefits of bupropion maleate over bupropion hydrochloride.
10 Bupropion is used primarily in the treatment of depression, which along with mania, falls under the heading of affective disorders. Particularly, bupropion is used in patients who do not respond to, or cannot tolerate other antidepressants, such as the tricyclic agents or monoamine
15 oxidase inhibitors. Additionally, the racemic mixture of bupropion is useful in the management of patients with bipolar and schizo-affective disorder, attention-deficit disorder, psycho-sexual dysfunction, bulimia and other eating disorders, and Parkinson's disease.
20 Affective disorders, including major depression, and the bipolar, manic-depressive illness, are characterized by changes in mood as the primary clinical manifestation. Major depression is the most common of the significant mental illnesses, and it must be distinguished clinically from
25 periods of normal grief, sadness and disappointment, and the related dysphoria or demoralization frequently associated with medical illness. Depression is characterized by feelings of intense sadness, and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and
30 self-deprecation. Physical changes can also occur, including insomnia, anorexia, and weight loss, decreased energy and libido, and disruption of hormonal circadian rhythms. Often the condition responds well to tricyclic or related antidepressant drugs, monoamine oxidase inhibitors, or in
35 resistant cases or severe disease, to electro-convulsive shock treatment.

Mania, as well as depression, is characterized by changes in mood as the primary symptom. Either of these two extremes of mood may be accompanied by psychosis with disordered thought and delusional perceptions. Psychosis may
5 have, as a secondary symptom, a change in mood, and it is this overlap with depression that causes much confusion in diagnosis. Severe mood changes without psychosis frequently occur in depression and are often accompanied by anxiety.

Through an unknown mechanism of action, bupropion
10 has been demonstrated to be an effective treatment in depression in short-term and longer duration clinical studies. The racemic mixture of bupropion has been reported to have an antidepressant activity equal to amitriptyline, the tricyclic antidepressant, with fewer anticholinergic,
15 sedative and cardiovascular side effects than with amitriptyline.

Parkinson's disease, independent of a specific etiology, is a chronic, progressive central nervous system disorder which usually appears insidiously in the latter
20 decades of life. The disease produces a slowly increasing disability in purposeful movement. It is characterized by four major clinical features of tremor, bradykinesia, rigidity and a disturbance of posture. Often patients have an accompanying dementia. In idiopathic Parkinsonism, there
25 is usually a loss of cells in the substantia nigra, locus ceruleus, and other pigmented neurons of the brain, and a decrease of dopamine content in nerve axon terminals of cells projecting from the substantia nigra. The understanding that Parkinsonism is a syndrome of dopamine deficiency and the
30 discovery of levodopa as an important drug for the treatment of the disease were the logical culmination of a series of related basic and clinical observations, which serves as the rationale for drug treatment.

When the racemic mixture of bupropion is used to
35 treat Parkinson's disease, an improvement in gait, akinesia, and postural stability were observed, with tremor improving in those patients experiencing the most global benefit.

Concomitant depression was alleviated in several of the patients reporting the condition.

Attention-deficit disorder ("ADD") is a common behavioral learning disorder in children which adversely affects school performance and family relationships. Symptoms and signs include hyperactivity (e.g., ADDH and AD/HD, DSM-IV), impulsivity, emotional lability, motor incoordination and some perceptual difficulties. Treatment has included psychostimulants, which while effective are controversial, and may cause troubling side effects such as dysphoria, headache and growth retardation. Other drugs, including the tricyclic antidepressants, appear to improve attention, but may be less effective than the psychostimulants.

Bupropion has been shown to be effective in children with attention-deficit disorder or conduct disorder thus improving the symptoms of anxiety, hostility and uncooperativeness, antisocial behavior, as well as eating disturbances. The drug has also demonstrated activity in cases of psycho-sexual dysfunction and bulimia. However, bupropion is contra-indicated in patients with a seizure disorder, or a current or prior diagnosis of bulimia or anorexia nervosa characterized by a disturbed sense of body image and abnormally high anxiety about weight gain.

It has been suggested that the racemic mixture of bupropion could be used to assist in weight loss. Treatment with bupropion is consistently associated with a lack of weight gain. Also bupropion reduces episodes of binge eating and purging. Although the mechanism by which bupropion causes weight loss is uncertain, an increase in the activity of the patient may play some part together with subtle changes in food intake and metabolism.

The causes of excess body weight and/or obesity are complex; however, a common denominator in the overweight person's diet is a caloric intake which exceeds that person's body expenditures. One method of treating a person who is overweight and/or obese is to restrict that person's caloric

intake, in combination with an exercise regimen. This method may be limited in its effectiveness since many overweight or obese people have developed eating and activity patterns which are counterproductive to achieving weight reduction.

5 Another method to treat overweight or obese patients is to administer appetite suppressant drugs in conjunction with a weight reduction program. The drawback to this method is that many appetite suppressant drugs produce undesirable adverse effects which limit their usefulness.

10 The racemic mixture of bupropion, in addition to its use in the treatment of depression and the other above-mentioned disorders, has been shown to have a wide spectrum of action which includes:

- 15 -- Treatment of the effects of ethanol (U.S. Patent No. 4,393,078)
- Treatment of Tardive Dyskinesia (U.S. Patent No. 4,425,363)
- Treatment of Minimal Brain Dysfunction (U.S. Patent No. 4,435,449)
- 20 -- Treatment of amelioration of prostate hypertrophy and sexual dysfunction (U.S. Patent No. 4,835,147)
- Treatment of psychostimulant addiction (U.S. Patent No. 4,935,429)
- 25 -- Treatment of Psychosexual Dysfunction (U.S. Patent No. 4,507,323)
- Methods of Reducing Cholesterol (U.S. Patent No. 4,438,138)
- Methods of assisting weight loss (U.S. Patent No. 4,895,845)
- 30

The racemic mixture of bupropion has been shown to have certain advantages over other antidepressant drugs. For example, bupropion does not inhibit monoamine oxidase, or block the reuptake of serotonin. At therapeutic
35 concentrations, the compound presumably does not bind to adrenergic, dopamine, GABA, histamine, muscarinic, serotonin, or imipramine binding sites. While its specific

neurochemical antidepressant action is unknown, it does have a relatively weak effect on blocking the reuptake of dopamine, and it appears to reduce norepinephrine metabolism.

While the racemic mixture of bupropion has 5 advantages, it also has disadvantages. Among these disadvantages are adverse effects in addition to those described above. The most serious adverse effect associated with the racemic mixture of bupropion is the increased incidence of seizures. In addition, other frequently 10 reported adverse effects associated with the use of racemic bupropion include nausea, vomiting, excitement, agitation, blurred vision, restlessness, postural tremor, and some hallucinations/confusional states with the potential for abuse. Other adverse or side effects associated with the 15 racemic mixture of bupropion include but are not limited to anxiety, insomnia, headaches and/or migraines, dry mouth, constipation, tremor, sleeping disturbances, dermatologic problems (e.g., rashes), neuropsychiatric signs and symptoms (e.g., delusions and paranoia), and weight loss or gain. 20 See, the Physician's Desk Reference® (1998). These effects are dose limiting in a number of patients. In Parkinsonian patients, the adverse effects can be the particular toxicity of the racemic mixture of bupropion or the result of a drug interaction (as most patients were receiving concomitant 25 levodopa).

Thus, it is desirable to find a compound with the advantages of the racemic mixture of bupropion without the above-described disadvantages.

30

35

25
1032

3. SUMMARY OF THE INVENTION

The active compound of compositions and methods disclosed herein is an optical isomer of the compound bupropion which is described in United States Patent Nos. 3,819,706 and 3,885,046. Chemically, this isomer is (+)-2-(tertbutylamino)-3'-chloropropiophenone or (+)-1-(3-chlorophenyl)-2[(1,1-dimethyl-ethyl)amino]-1-propanone. This isomer will hereinafter be referred to as "(+)-bupropion", which also includes the substantially optically pure (+)-bupropion isomer.

It has now been discovered that the optically pure (+)-isomer of bupropion is an effective antidepressant which is useful in treating depression in humans. In accordance with the present invention, (+)-bupropion can be used to treat depression while avoiding adverse effects including but not limited to seizures, agitation, dry mouth, insomnia, headache/migraine, nausea, dizziness, tachycardia, vomiting, constipation, and tremor associated with the racemic mixture of bupropion. It has also been discovered that (+)-bupropion and pharmaceutical compositions containing optically pure (+)-bupropion are useful in treating weight gain or obesity. Furthermore, it has been discovered that the optically pure (+)-isomer of bupropion is useful in the treatment of Parkinson's disease. In addition, it has been found that the optically pure (+)-isomer is useful in the treatment of other disorders including but not limited to bipolar disorders, attention-deficit disorders, conduct disorders, psycho-sexual dysfunction, bulimia, eating disorders and specific food cravings.

The present invention also includes methods for treating the above-described conditions in a human while avoiding adverse effects that are associated with the racemic mixture of bupropion, by administering the optically pure (+)-isomer of bupropion to said human.

26
1033

4. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating depression in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic bupropion which comprises administering to said human in need of antidepressant therapy, an amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, said amount being sufficient to alleviate depression, but insufficient to cause adverse effects associated with racemic bupropion.

The present invention also encompasses pharmaceutical compositions for the treatment of humans which comprises a therapeutically effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, and a pharmaceutically acceptable carrier. Preferred pharmaceutical compositions are those which have a means for controlled sustained release of the active ingredient, (+)-bupropion.

The present invention further encompasses a method of treating Parkinson's disease in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic bupropion, which comprises administering to said human suffering from Parkinson's disease, an amount of (+)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, said amount being sufficient to alleviate said condition, but insufficient to cause adverse effects associated with administration of racemic bupropion.

Further, the present invention encompasses a method of treating obesity or weight gain in a human, which comprises administering to said human in need of a reduction in weight, an amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, said amount being sufficient to reduce weight or prevent weight gain, but insufficient to cause adverse effects associated with administration of racemic bupropion.

29
103-

The present invention also encompasses a method of treating disorders including, but not limited to, bipolar disorders, attention-deficit disorders, conduct disorders, psycho-sexual dysfunction, bulimia, eating disorders and
5 specific food cravings in humans while avoiding the concomitant liability of adverse affects associated with the administration of racemic bupropion, which comprises administering to a human in need of such therapy a therapeutically effective amount of (+)-bupropion, or a
10 pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer.

The racemic mixture of bupropion (i.e., approximately a 50:50 mixture of its two enantiomers) causes antidepressant activity and provides therapy and/or reduction
15 of symptoms in a variety of conditions and disorders; however, this racemic mixture, while offering the expectation of efficacy, causes a broad range of adverse effects. Utilizing the optically pure (+)-isomer of bupropion results in clearer dose-related definitions of efficacy, diminished
20 adverse effects, and accordingly an improved therapeutic index. It is therefore, more desirable to use the (+)-isomer of bupropion for the conditions described herein.

The term "adverse effects" as used herein includes, but is not limited to seizures, dry mouth, insomnia,
25 dizziness, restlessness, anxiety, agitation, headache/migraine, nausea/vomiting, constipation, tremor, delusions, tachycardia, hallucinations, psychotic episodes, blurred vision, confusion, paranoia, rashes and sleep disturbances.

30 The term "substantially free of the (-)-stereoisomer" as used herein means that the composition contains a greater proportion of the (+)-isomer of bupropion in relation to the (-)-isomer of bupropion. In a preferred embodiment the term "substantially free of its (-)-isomer" as
35 used herein means that the composition contains at least 90% by weight of (+)-bupropion and 10% by weight or less of (-)-bupropion; or more preferably about 95% by weight of (+)-

28
10.1

bupropion and 5% or less of its (-)-isomer. These percentages are based on the total amount of bupropion present in the composition. In the most preferred embodiment the term "substantially free of the (-)-stereoisomer" means
5 that the composition contains approximately 99% by weight of (+)-bupropion, and 1% or less of the (-)-bupropion. In another preferred embodiment, the term "substantially free of its (+)-stereoisomer" as used herein means that the composition contains greater than 99% by weight of the (+)-
10 isomer of bupropion, again based on the total amount of bupropion present. The terms "substantially optically pure (+)-isomer of bupropion," "optically pure (+)-isomer of bupropion" and "(+)-isomer of bupropion" are also encompassed by the above-described amounts.

15 The term "a method of treating depression" as used herein means relief from the symptoms of depression which include, but are not limited to changes in mood, feelings of intense sadness and despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-
20 deprecation. Physical changes may also be relieved, including insomnia, anorexia and weight loss, decreased energy and libido, and the return of normal hormonal circadian rhythms.

The term "attention deficit disorder" (ADD) and
25 "attention deficit disorder with hyperactivity" (ADHD), DSM-III, or attention deficit/hyperactivity disorder (AD/HD), DSM-IV are used herein mean in accordance with the accepted meanings.

The term "treating Parkinson's disease" as used
30 herein means relief from the symptoms of Parkinson's disease which include, but are not limited to tremor, bradykinesia, rigidity, and a disturbance of posture.

The term "treating obesity or weight gain in a human" as used herein means reduction of weight or relief
35 from being overweight or gaining weight due to extensive consumption of food and other factors including metabolism disorders.

29
1036

4.1. SYNTHESIS OF OPTICALLY PURE BUPROPION

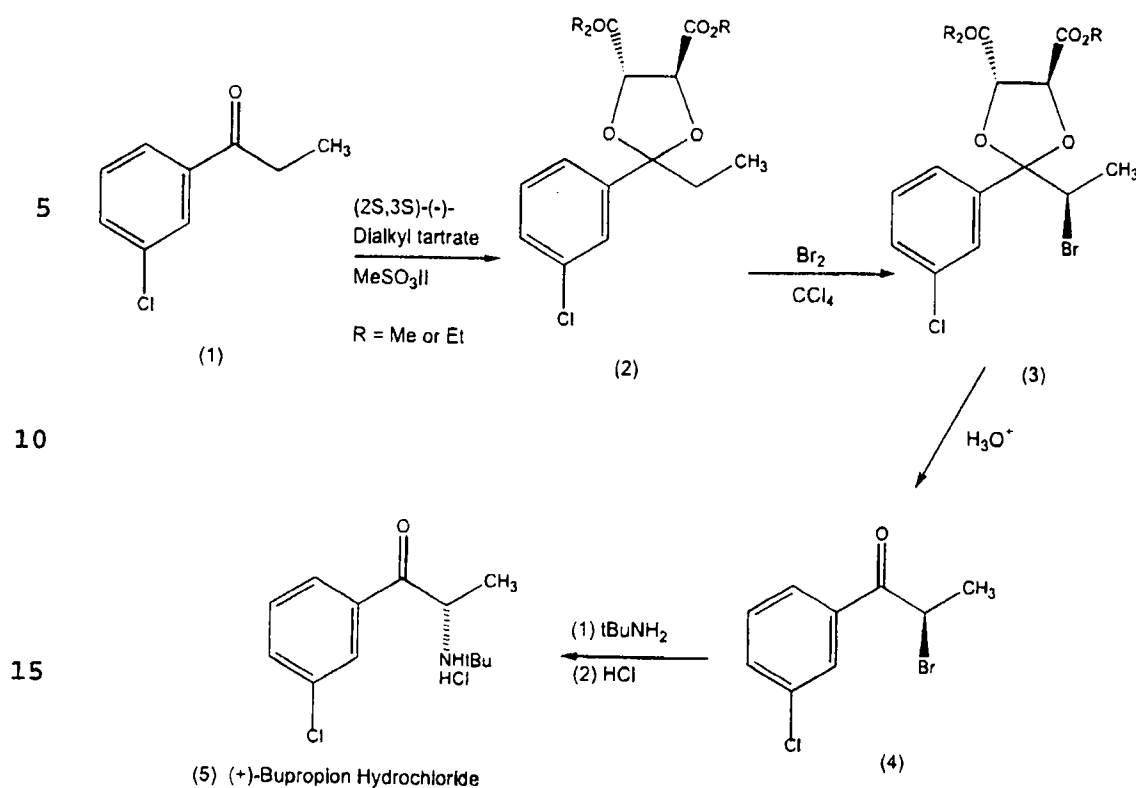
The synthesis of the (+)-isomer of bupropion may start from readily available 3-chloropropiophenone (1).

- 5 Reaction of (1) with a (2S,3S)-(-)-dialkyl tartrate such as (-)-dimethyl or diethyl tartrate in the presence of an acid catalyst such as methanesulfonic acid gives the chiral acetal (2) according to Castaldi (G. Castaldi, et al., *J. Org. Chem.* 1987, 52: 3018). Stereoselective bromination with bromine in
10 carbon tetrachloride (or alternatively in ethyl acetate) then produces the corresponding bromoacetal (3) as the major product according to the above-referenced procedure developed by Castaldi and co-workers. The bromoacetal (3) is purified by column chromatography to yield the optically pure
15 bromoacetal (3) which is then hydrolyzed in the presence of an acid to afford the bromoketone (4). Treatment of the bromoketone (4) with tert-butylamine, followed by reaction with anhydrous hydrogen chloride, then produces optically pure (+)-bupropion hydrochloride (5) after recrystallization.
20 See the scheme below.

25

30

35



20 Alternatively, the optically pure isomers of bupropion can be prepared by another asymmetric route according to the procedures reported by Musso et al., "Synthesis and Evaluation of the Antidepressant Activity of the Enantiomers of Bupropion", *Chirality* 5:495-500 (1993) which is incorporated herein by reference in its entirety.

In addition to the above-described methods the stereoisomers of bupropion may be obtained by resolutions of a mixture of enantiomers of bupropion using conventional means such as an optically active resolving agent; see, for example, "Stereochemistry of Carbon Compounds", by E.L. Eliel (McGraw-Hill, NY, 1962), and S.H. Wilen, p. 268 in "Tables of Resolving Agents and Optical Resolutions" (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

The magnitude of a prophylactic or therapeutic dose of (+)-bupropion in the acute or chronic management of disease will vary with the severity of the condition to be treated and its route of administration. The dose and dose

frequency will also vary according to the age, weight, condition and response of the individual patient. In general, the recommended daily dose range for the conditions described herein lies within the range of from about 10 mg to 5 about 750 mg per day, generally divided equally into doses given three or four times a day. Preferably, a daily dose range should be between 50 mg and 600 mg per day, usually divided equally into a three or four times a day dosing. Most preferably, a daily dose range should be between 60 mg 10 and 450 mg per day, usually divided equally into a three times or a four times a day dosing. It may be necessary to use dosages outside these ranges in some cases. The physician will know how to increase, decrease or interrupt treatment based upon patient response. The various terms 15 described above such as "said amount being sufficient to alleviate said depression", "said amount being sufficient to alleviate said condition" when said condition is Parkinson's Disease, "said amount being sufficient to reduce weight or weight gain", "said amount being sufficient to achieve weight 20 loss" and "therapeutically effective amount" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage 25 of (+)-bupropion. For example, oral, rectal, parenteral, transdermal, subcutaneous, intrathecal, intramuscular and the like may be employed as appropriate. Dosage forms include tablets, coated tablets, caplets, capsules, troches, dispersions, sustained release formulations, suspensions, 30 solutions, patches and the like.

The pharmaceutical compositions of the present invention comprise the (+)-isomer of bupropion as active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and 35 optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared

from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable
5 non-toxic acids including inorganic and organic acids. Such acids include maleic, acetic, benzene-sulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic,
10 nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are hydrobromic, hydrochloric, phosphoric, and sulfuric acids.

The pharmaceutical compositions of the present
15 invention include compositions suitable for oral, rectal, and parenteral administration (including subcutaneous, intrathecal, intramuscular, and intravenous), although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most
20 preferred route of the present invention is the oral route. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In the case where an oral composition is employed,
25 a suitable dosage range for use is, e.g., from about 10 mg to about 750 mg per day, generally divided equally into a three times a day dosing, preferably from about 50 mg to about 600 mg per day, generally divided equally into a three times a day dosing and most preferably from about 60 mg to about 450
30 mg per day, generally divided equally into a three times a day dosing. Patients may be upward titrated from below to within this dose range to a satisfactory control of symptoms, or blood pressure as appropriate.

In practical use, (+)-bupropion can be combined as
35 the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take

a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form, any of the
 5 usual pharmaceutical media may be employed, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, for example, suspensions, elixirs and solutions; or aerosols; or carriers such as starches,
 10 sugars, microcrystalline cellulose, stabilizers, diluents, granulating agents, lubricants, binders, fillers, disintegrating agents and the like in the case of oral solid preparations such as, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid
 15 preparations. The preferred solid oral preparation is tablets. The most preferred solid oral preparation is coated tablets. Because of their ease of administration tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are
 20 obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical stabilizers may also be used to stabilize compositions containing (+)-bupropion or salts thereof; acceptable stabilizers including but are not limited
 25 to L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabsulfite, citric acid, tartaric acid and L-cystine dihydrochloride. See, e.g., U.S. Patent No. 5,358,970 which is incorporated herein by reference.

In addition to the common dosage forms set out
 30 above, the compounds of the present invention may also be administered by controlled release or sustained release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200, 4,008,719, 4,687,660, and 4,769,027, the
 35 disclosures of which are hereby incorporated by reference. Preferred controlled release or sustained released tablets

for use with (+)-bupropion are described in U.S. Patent No. 5,427,798 which is incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented
5 as discrete units such as capsules, cachets, or tablets or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion.
10 Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately
15 admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients.
20 Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, filler, lubricant, inert diluent, and/or surface active or dispersing agent. Molded tablets may be made by molding in a
25 suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 10 mg to about 250 mg of the active ingredient, and each cachet or capsule contains from about 10 mg to about 250 mg of the active ingredient. Most
30 preferably, the tablet, cachet or capsule contains one of four dosages: about 50 mg, about 75 mg, about 100 mg and about 150 mg of active ingredient.

The invention is further defined by reference to the following examples describing in detail the preparation
35 of the compound and compositions of the present invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be

practiced without departing from the purpose and interest of this invention.

All temperatures are in degrees Celsius.

5

5. EXAMPLES

5.1. EXAMPLE 1

ORAL FORMULATION

Coated Tablets:

10 Formula	Quantity per Tablet (mg.)
(+)-bupropion	75
Lactose	125
Corn Starch	5.0
15 Water (per thousand Tablets)	30.0 ml *
Magnesium Stearate	0.5
Corn Starch	25.0

*

20 The water evaporates during manufacture.

25 The active ingredient is blended with the lactose until a uniform blend is formed. The smaller quantity of corn starch is blended with a suitable quantity of water to form a corn starch paste. This is then mixed with said uniform blend until a uniform wet mass is formed. The remaining corn starch is added to the resulting wet mass and mix until uniform granules are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch stainless steel screen. The milled granules are then dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are then milled through a suitable milling machine using 1/4 mesh stainless steel screen. The magnesium stearate is then blended and the resulting mixture is compressed into tablets of desired shape, thickness, hardness and disintegration. Tablets are coated by standard aqueous or nonaqueous techniques.

36
10425.2. EXAMPLE 2ORAL FORMULATIONCapsules:

Formula	Quantity per capsule in mg.		
	<u>A</u>	<u>B</u>	<u>C</u>
Active ingredient	25	50	75
10 (+)-bupropion			
Lactose	149.5	124.5	374
Corn Starch	25	25	50
Magnesium Stearate	0.5	0.5	1.0
Compression Weight	200.0	200.0	500.0

15 The active ingredient, (+)-bupropion, lactose, and corn starch are blended until uniform; then the magnesium stearate is blended into the resulting powder. The resulting mixture is encapsulated into suitably sized two-piece hard gelatin capsules.

20

5.3. EXAMPLE 3ORAL FORMULATIONTablets

Formula	Quantity per Tablet in mg.		
	<u>A</u>	<u>B</u>	<u>C</u>
Active ingredient,	20	40	100
(+)-bupropion			
lactose BP	134.5	114.5	309.0
30 starch BP	30.0	30.0	60.0
Pregelatinized Maize Starch BP	15.0	15.0	30.0
magnesium stearate	0.5	0.5	1.0
Compression Weight	200.0	200.0	500.0

The active ingredient is sieved through a suitable
 35 sieve and blended with lactose, starch, and pregelatinized maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules

37
043

are screened and blended with the magnesium stearate. The granules are then compressed into tablets using punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

5.4. EXAMPLE 4

Sustained Release Formulation (Tablet)

10	FORMULA	QUANTITY PER TABLET (mg)
	(+)-bupropion hydrochloride	100
	Contramid® crosslinked amylose	98.8
	Cysteine hydrochloride	7.5
15	Magnesium stearate	1.2

(+)-Bupropion Hydrochloride is formulated using Contramid® (Labopharm, Inc, Quebec) technology. The formulation is prepared by blending the ingredients above (dry) and compressing into tablets. Alternatively, the ingredients can be formulated using wet granulation technology known in the art. (See Example 1).

5.5. EXAMPLE 5

Sustained Release Formulation (Tablet)

25	FORMULA	QUANTITY PER TABLET (mg)
	Contramid® crosslinked amylose	98.8
	Cysteine hydrochloride	7.5
	(+)-bupropion hydrochloride	75
30	Magnesium stearate	1.2

(+)-Bupropion Hydrochloride is formulated using Contramid® (Labopharm, Inc, Quebec), technology. The formulation is prepared by blending the ingredients above (dry) and compressing into tablets. Alternatively, the ingredients can be formulated using wet granulation technology known in the art. (See Example 1).

5.6. EXAMPLE 6

FORMULA	QUANTITY PER TABLET (mg)
(+)-bupropion hydrochloride	150
5 Diffutab® hydrophilic polymer mixture	100
Microcrystalline cellulose	100
Cysteine hydrochloride	7.5
10 Magnesium stearate	4

(+)-Bupropion Hydrochloride is formulated using Diffutab® (Eurand, Microencapsulation, S.A. of Switzerland) technology. The formulation components are dry blended and directly compressed into tablets or formulated using wet granulation technology.

The embodiments of the present invention described above are intended to be merely exemplary and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present invention and are covered by the following claims.

The contents of all references described herein are hereby incorporated by reference.

Other embodiments are within the following claims.

39
215

What is claimed is:

1. A method of treating depression in a human while avoiding the concomitant liability of adverse effects associated with administration of racemic bupropion, which
5 comprises administering to a human in need of antidepressant therapy, a therapeutically effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer.
- 10 2. The method of claim 1 wherein said amount is sufficient to alleviate said depression, but insufficient to cause said adverse effects associated with administration of racemic bupropion.
- 15 3. The method of claim 1 wherein (+)-bupropion is administered intravenously, transdermally or orally.
4. The method of claim 3 wherein (+)-bupropion is administered orally as a tablet or a capsule.
- 20 5. The method of claim 1 wherein the amount administered is from about 10 mg to about 750 mg.
6. The method of claim 5 wherein the amount
25 administered is from about 50 mg to about 600 mg.
7. The method of claim 6 wherein the amount administered is from about 60 mg to about 450 mg.
- 30 8. The method of claim 1 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.
- 35 9. The method of claim 1 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof,

40
1060

substantially free of its (-)-stereoisomer is administered together with a pharmaceutically acceptable carrier.

10. The method according to claim 1 wherein
5 (+)-bupropion is administered as the hydrochloride salt.

11. The method of claim 1 wherein (+)-bupropion is administered in a sustained or controlled release formation.

10 12. A method of treating Parkinson's disease in a human while avoiding the concomitant liability of adverse effects associated with the administration of racemic bupropion, which comprises administering to said human in need of treatment for Parkinson's disease, a therapeutically
15 effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer.

13. The method of claim 12, wherein said said amount
20 is sufficient to alleviate said disease, but insufficient to cause said adverse effects associated with administration of racemic bupropion.

14. The method of claim 12 wherein (+)-bupropion is
25 administered by intravenously, transdermally, or orally.

15. The method of claim 14 wherein (+)-bupropion is administered orally as a tablet or a capsule.

30 16. The method of claim 12 wherein the amount administered is from about 10 mg to about 750 mg.

17. The method of claim 16 wherein the amount administered is from about 50 mg to about 600 mg.
35

18. The method of claim 17 wherein the amount administered is from about 60 mg to about 450 mg.

41
1047

19. The method of claim 12 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.

5

20. The method of claim 12 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

10

21. The method according to claim 12 wherein (+)-bupropion is administered as the hydrochloride salt.

22. The method of claim 12 wherein (+)-bupropion is administered in a sustained or controlled release formulation.

23. A method for treating obesity or weight gain in a human which comprises administering to a human in need of weight reduction or weight control a therapeutically effective amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer

24. The method of claim 23 wherein said amount is sufficient to alleviate obesity or weight gain, but insufficient to cause adverse effects associated with administration of racemic bupropion.

25. The method of claim 23 wherein (+)-bupropion is administered by intravenously, transdermally, or orally.

26. The method of claim 25 wherein (+)-bupropion is administered orally as a tablet or a capsule.

35

27. The method of claim 23 wherein the amount administered is from about 10 mg to about 750 mg.

42
1048

28. The method of claim 27 wherein the amount administered is from about 50 mg to about 600 mg.

29. The method of claim 28 wherein the amount administered is from about 60 mg to about 450 mg.

30. The method of claim 23 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.

31. The method of claim 23 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

32. The method according to claim 23 wherein (+)-bupropion is administered as the hydrochloride salt.

33. The method of claim 23 wherein (+)-bupropion is administered in a sustained release or controlled release formulation.

34. A method of treating a disorder selected from the group consisting of bipolar disorders, attention-deficit disorders, conduct disorders, psycho-sexual dysfunction, bulimia, eating disorders and specific food craving which comprises administering to a human suffering from said disorder a therapeutically effective amount of (+)-bupropion, or a pharmaceutically acceptable salt therefore, substantially free of its (-)-stereoisomer.

35. The method of claim 34 wherein (+)-bupropion is administered by intravenously, transdermally, or orally.

36. The method of claim 35 wherein (+)-bupropion is administered orally as a tablet or a capsule.

43
10-19

37. The method of claim 34 wherein the amount administered is from about 10 mg to about 750 mg.

38. The method of claim 37 wherein the amount administered is from about 50 mg to about 600 mg.

39. The method of claim 38 wherein the amount administered is from about 60 mg to about 450 mg.

10 40. The method of claim 34 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of bupropion.

15 41. The method of claim 34 wherein the amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (-)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

20 42. The method according to claim 34 wherein (+)-bupropion is administered as the hydrochloride salt.

43. The method of claim 34 wherein (+)-bupropion is administered in a controlled or sustained release
25 formulation.

44. A pharmaceutical composition which comprises a therapeutically amount of (+)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its
30 (-)-stereoisomer, and a pharmaceutically acceptable carrier.

45. The composition according to claim 44 wherein the amount is about 10 mg to about 750 mg.

35 46. The composition according to claim 44 which comprises (+)-bupropion hydrochloride.

44
10/50

47. The composition according to claim 46 wherein said composition is adapted for oral administration.

48. The composition according to claim 46 adapted for 5 intravenous delivery.

49. The composition according to claim 46 for use in a transdermal formulation.

10 50. The composition according to claim 46 for use as a transdermal patch.

51. The composition of claim 46 wherein said composition is a solid preparation.

15

52. A sustained release formulation which comprises (+)-bupropion or a pharmaceutically acceptable salt thereof substantially free of its (-)-stereoisomer, and a pharmaceutically acceptable carrier.

20

53. The sustained release formulation of claim 52 wherein said formulation is a tablet, capsule or gelcap.

25

30

35